REMARKS

Claims 1-48 are pending in the present application prior to the amendments made herewith. By amendment herewith, Claims 1, 3, 10, 11, 12, 13, 17, 38, 39, 40, 46 and 47 are being changed; and new Claims 77-86 are being added. The amendments introduce no new matter.

It is noted that Claims 3-6 and 14-18 are rejected only under a provisional rejection based on obviousness-type double patenting and that Claim 19 has not been rejected at all, indicating identification by the Examiner of allowable subject matter at least in Claims 3-6 and 14-19.

Initially, appreciation is expressed for the Examiner taking a few minutes in a telephone conference on July 3, 2003 to discuss the pending claims in relation to the rejections in the January 15, 2003 Office Action.

Each of the issues raised by the Examiner in the January 15, 2003 Office Action will now be addressed.

The Examiner states that the specification on page 1 should be updated to reflect the status and relationship between the present application and application 09/740,573. Application 09/740,573 claims priority to the present application pursuant to 35 U.S.C. § 120. Although 35 U.S.C. § 120 requires that application 09/740,573 must contain a reference to the present application, the undersigned is not aware of any requirement that application 09/740,573 must be referenced in the present application, and accordingly no such reference has been made. If the Examiner asserts that such a reference is required, the Examiner is respectfully requested to specify the basis (e.g. statute or rule) for the requirement.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects Claims 10, 11-13, 17, 40, 41, 46 and 47 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The rejection is traversed. Nevertheless, Claims 10, 17, 39, 40, 46 and 47 have been amended to obviate the rejection.

In Claim 10, the Examiner specifically objects to a lack of units for "0.8" and "0.95", and in stating the objections the Examiner also noted Claims 11, 40 and 41. As discussed in the application, *inter alia*, at page 10, line 16 through page 11, line 11, reduced pressure and reduced temperature are dimensionless pressure and temperature ratios relative to the critical pressure and

critical temperature, respectively, of a fluid. Claims 10, 39 and 40 have been amended to expressly state in the claims the definitions for "reduced pressure" and "reduced temperature" already applicable to these terms. These amendments are neither narrowing nor made for any purpose related to patentability.

In Claim 17, the Examiner specifically objects to the terminology "if at all," for being an optional conditional phase. So long as language of a claim is clear and unambiguous, the undersigned is not aware of any prohibition or the use of optional or conditional text. Nevertheless, Claim 17 has been amended to remove the objected to text, stating instead that the cosolvent system comprises up to 5 weight percent water. The amendment is neither narrowing nor made for any reason related to patentability. It is noted that the term "up to" is recognized as stating a range including zero as a lower limit. See MPEP § 2173.05(c), citing to *In re Mochel*, 470 F.2d 638, 176 USPQ 194 (CCPA 1974).

In Claims 46 and 47, the Examiner specifically objects to the use of the word "percent" as being unclear as to what type of percent, "e.g., molarity percent or weight percent or volume percent". Claims 46 and 47 have been amended to state that the percent is on a weight basis, consistent with a discussion concerning degree of insulin encapsulation presented in the application at page 29, line 7 through page 30, line 14. The amendments are neither narrowing nor made for any reason related to patentability.

The rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claim Rejection Under 35 U.S.C. § 102 (b)

The Examiner rejects Claims 1-2, 7-13, 20-29, 42-44 and 48 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,770,559 to Manning et al. The rejection is traversed.

Claim 1 has been amended to recite "separating the particles from the first organic solvent, the second organic solvent and the anti-solvent fluid." A discussion concerning separation of particles from the first organic solvent, the second organic solvent and the anti-solvent fluid is presented in the specification, *inter alia*, at page 9, lines 6-10.

Claim 1 is directed to a method for making a particulate product containing insulin, and requires a specific combination of processing features, including contacting a feed solution containing insulin with a compressed anti-solvent fluid to precipitate particles containing insulin. In the feed solution, the insulin is in a cosolvent system comprising different first and second

organic solvents that are mutually soluble. Also, the precipitated particles are separated from the first organic solvent, the second organic solvent and the anti-solvent fluid.

The co-solvent system (including the first and second organic solvents) used with the invention is a process fluid that facilitates precipitation of insulin-containing particles when contacted with the compressed anti-solvent fluid. Neither the first organic solvent nor the second organic solvent is to be a component of the precipitated particles. Rather, the precipitated insulin-containing particles are separated from process fluid including the compressed anti-solvent fluid and the first and second organic solvents. With the present invention, the particles may have very little, if any, residual solvent contamination.

Among other things, the Examiner points to disclosure in Manning et al. concerning the use of sodium dodecyl sulfate (SDS) and dimethyl formamide (DMF) and asserts that these materials satisfy the first organic solvent and second organic solvent limitations, respectively, of Claim 1.

In that regard, Manning et al. disclose a method, which is summarized at column 3, lines 2-9, as follows:

> According to the present invention, a method is provided for placing a pharmaceutical substance into solution in an organic solvent in the form of a hydrophobic ion pair complex with an amphiphilic material. The resulting solution may then be subjected to gas anti-solvent precipitation using a near critical or supercritical fluid to produce a precipitate of particles comprising the pharmaceutical substance.

Manning et al. distinguish between the hydrophobic ion pair complex, which is formed by the pharmaceutical substance and the amphiphilic material, and the organic solvent, in which the hydrophobic ion pair complex is dissolved. In a discussion at column 6, lines 33-47, Manning et al. disclose that SDS may be used as the amphiphilic material. The SDS is not disclosed as being an organic solvent in the nature of the first and second organic solvents of a cosolvent system in the combination of processing features recited in Claim 1. Examples, including DMF, for the "organic solvent" of Manning et al. are listed at column 7, lines 3-18.

Moreover, at column 11, lines 39-43, Manning et al. disclose:

> During the antisolvent precipitation 104, the antisolvent fluid 106 invades the organic solvent of the liquid feed solution 102, resulting in precipitation of solid particles comprising the pharmaceutical substance and the amphiphilic material. [Emphasis added.]

This is significantly different than the first organic solvent and the second organic solvent recited in the combination of Claim 1, which are both separated, along with the compressed anti-solvent fluid, from the precipitated insulin-containing particles. Manning et al. do not disclose the combination of processing features recited in Claim 1. Moreover, each of the pending dependent claims recites additional limitation(s) that further distinguish over Manning et al.

The rejection under 35 U.S.C. § 102(b) should be withdrawn.

Claim Rejection Under 35 U.S.C. § 103(a)

The Examiner rejects Claims 1-2, 7-13, 20-48 under 35 U.S.C. § 103(a) as being obvious over Manning, et al. taken with U.S. Patent No. 6,063,910 to Debenedetti et al. and U.S. Patent No. 6,372,260 to Andersson et al. The rejection is traversed.

It is noted that there does not appear to be any suggestion, motivation or teaching in any of Manning et al., DeBennedetti et al. or Andersson et al. for combining the teachings of those references, even though the references may, in one respect, all discuss supercritical anti-solvent processing to precipitate drug-containing particles. As noted above, Manning et al. concerns the use of amphiphilic materials to form with a pharmaceutical substance a hydrophobic ion pair complex that is soluble in certain organic solvents, and discuss processing such solutions of the hydrophobic ion pair complex by supercritical anti-solvent processing to precipitate particles including the pharmaceutical substance and the amphiphilic material. DeBennedetti et al. and Andersson et al., likewise each disclose their own anti-solvent precipitation techniques, but there is no suggestion, motivation or teaching in any of the references that would lead one of ordinary skill in the art to selectively extract and recombine in a particular way features from each of the different references, because each reference discloses a complete process unto itself, with no indication of further needs in relation to successful anti-solvent processing.

However, even assuming solely for the sake of argument that the teachings of the references are properly combinable, none of Manning et al., DeBennedetti et al. or Anderson et al., alone or in combination with each other, disclose an anti-solvent precipitation process using a cosolvent system comprising first and second organic solvents that are separated with the compressed anti-solvent fluid from the particles following precipitation of insulin-containing particles, let alone in the specific combinations of the pending claims.

The rejection under 35 U.S.C. § 103(a) should be withdrawn.

Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejects Claims 1-18 under the judicially created doctrine of obviousness-type double patenting over claims in copending application 09/740,573. Currently, no claims are allowed in application 09/740,573. If claims become allowed in application 09/740,573, then filing of a terminal disclaimer in the instant application will be considered to address the obviousness-type double patenting objection raised by the Examiner.

It is believed that all of the issues raised in the Office Action have been addressed herein. Should the Examiner maintain any of the rejections of any of the pending claims under 35 U.S.C. § 102(b) or 103(a), it is respectfully requested that it be pointed out with particularity how the cited reference(s) meet each and every term of each claim with respect to which rejection is maintained. In the absence of a persuasive showing to that effect, all pending claims should be allowed.

A petition for a three-month extension of time is enclosed herewith along with a check for $465 for the fee under 37 C.F.R. § 1.17(a)(3). No additional fees are believed to be due with this communication. If, however, any additional fees are due, please debit such fees to Deposit Account No. 50-1419. Credit any over payments to Deposit Account No. 50-1419.

The application is believed to be in condition for allowance and allowance of all pending claims is earnestly requested. If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented, or to discuss possible Examiner amendments to further prosecution of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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